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Pandemic Influenza and Pregnant Women: Summary of a Meeting of Experts

Pandemic Influenza: Special Considerations for Pregnant Women was a meeting convened by the Centers for Disease Control and Prevention in 2008 to obtain input from experts and key partners regarding clinical management of pregnant women and related public health actions to be taken during a pandemic.

Meeting goals were to discuss issues specific to pregnant women, identify gaps in knowledge, and develop a public health approach for pregnant women in the event of a pandemic. The meeting focused on 4 main topics: prophylaxis and treatment with influenza antiviral and other medications, vaccine use, nonpharmaceutical interventions and health care planning, and communications.

Participants reviewed the available evidence to guide action in each of these areas and identified areas of critical needs for future research. (*Am J Public Health.* 2009;99: S248–S254. doi:10.2105/AJPH.2008.152900)

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PREGNANT WOMEN CONSTITUTE a significant population in the United States: more than 6 million pregnancies occurred in 2004.¹ Plans for an influenza pandemic should address several issues specific to pregnant women to ensure that they receive appropriate guidance and health care.² Experience with previous pandemics and with seasonal influenza has led health care professionals to anticipate that pregnant women will be at increased risk for influenza-associated morbidity and mortality in a future pandemic.^{3–8} The public health response should take into account the effects of maternal influenza infection and its associated fever, medications for prophylaxis and treatment, and influenza vaccine on both mother and fetus.

Pregnant women or their health care providers may be reluctant to adopt public health recommendations during a pandemic because of concerns about fetal effects of

medications or vaccines. Recommendations regarding nonpharmaceutical interventions may present special challenges to pregnant women because these may conflict with routine prenatal care and delivery recommendations. In addition, health care facilities need to develop plans to minimize exposure of well pregnant women to ill people, while continuing to ensure that women receive necessary obstetric care.² Finally, communicating recommendations in a pandemic to the diverse population of pregnant women and their health care providers will be challenging.²

The Centers for Disease Control and Prevention, in partnership with the Association of Maternal and Child Health Programs and the March of Dimes, convened Pandemic Influenza: Special Considerations for Pregnant Women, a meeting designed to integrate scientific evidence and expert opinion, on April 3 to 4, 2008, in Atlanta, Georgia. The meeting goals

were to discuss special considerations, identify important knowledge gaps, and obtain input from experts and key partners to guide the development of public health recommendations specific to pregnant women in the event of an influenza pandemic. In attendance were a wide variety of experts in obstetrics, maternal–fetal medicine, family medicine, preventive medicine, pediatrics, midwifery, teratology, pharmacology, influenza, infectious diseases and vaccines, public health, emergency response, health education, and communications and representatives from key partner groups (see the box on the next page).

Discussion focused on 4 topics: prophylaxis and treatment with antiviral and other medications, vaccine use, nonpharmaceutical interventions and health care planning, and communications. Although this meeting focused on pregnancy issues, participants noted that guidance for postpartum

Organizations Represented at the Pandemic Influenza: Special Considerations for Pregnant Women Meeting: Atlanta, GA, April 3–4, 2008

American Academy of Family Physicians
American Academy of Pediatrics
American College of Nurse-Midwives
American College of Obstetricians
and Gynecologists
American Pharmacists Association
Association of Maternal and Child
Health Programs
Association of State and Territorial
Health Officials
Association of Women's Health, Obstetric
and Neonatal Nurses
Council of State and Territorial Epidemiologists
Food and Drug Administration

March of Dimes
National Association of County and City Health
Officials
National Institutes of Health
Organization of
Teratology Information Specialists
Society for Maternal-Fetal Medicine
State health departments
Universities
World Health Organization

and breastfeeding mothers and their infants was also needed. The meeting focused specifically on planning for an influenza pandemic, and thus its discussions should not be extrapolated to non-pandemic conditions. The findings presented here are not formal recommendations, but the discussion points outlined may serve as a basis for future recommendations.

PROPHYLAXIS AND TREATMENT

Several physiologic changes occur during pregnancy that can affect disease pathogenesis or treatment options.^{9–11} These alterations must be considered during development of recommendations for prophylaxis and treatment during pregnancy. Drawing on experience from previous pandemics, health care professionals expect that pregnant women will be at increased risk for influenza-associated morbidity, mortality, and pregnancy loss.^{3,4} Pregnant women are known to be at increased risk of complications associated with seasonal influenza,^{5–8} but influenza's effects on

the fetus are less clear. Seasonal influenza virus appears to be transmitted across the placenta rarely, but highly pathogenic strains of influenza virus, such as avian influenza A(H5N1), could be more likely to be transmitted across the placenta.¹² The capacity for human vertical transmission of highly pathogenic strains of influenza was demonstrated in a recent study, with detection of viral genomic sequences in the placental cytotrophoblasts and fetal respiratory tract from a pregnant woman infected with avian influenza A(H5N1).¹³

One of the more well-studied adverse effects of influenza is its associated hyperthermia. A meta-analysis found that maternal hyperthermia during the first trimester was associated with a doubled risk of neural tube defects.¹⁴ Data are less certain for other birth defects and adverse outcomes, but associations have been documented in some studies.^{15–17} Two studies suggest that the risk for birth defects associated with fever might be mitigated by antipyretic medications or multivitamins that contain folic acid.^{15,18} The presence of maternal fever during labor has

been shown to be a risk factor for adverse neonatal and developmental outcomes, including neonatal seizures, encephalopathy, cerebral palsy, and neonatal death.^{19–21} Distinguishing the effects of the cause of fever from the hyperthermia itself is difficult. However, because of the risk that hyperthermia appears to pose to the fetus, fever in pregnant women should be treated. Acetaminophen appears to be the best option for treatment of fever during pregnancy (Table 1), although data on even this common exposure are limited.

Little is known about the effects of the four currently available anti-influenza medications on the fetus (Table 2). All four are classified by the Food and Drug Administration as category C medications (ie., animal studies have either shown an adverse effect or no animal studies have been done and no adequate and well-controlled studies in pregnant women are available).³⁶ However, considering the limited available evidence and the consequences of untreated influenza for the woman, any potential risk to the fetus appears to be outweighed by the benefits of anti-influenza medications. Therefore, no evidence

has yet been found to support recommending different care for pregnant women from that provided for treatment or prophylaxis of other high-risk populations. Pregnant women should be considered high priority for receipt of anti-influenza medications for treatment or prophylaxis, given their increased risk of influenza-associated morbidity and mortality. This guidance applies only during an influenza pandemic, not to the use of these medications in a nonpandemic situation.^{37,38} Additional safety data for use of these medications in pregnant women are urgently needed.

None of the four anti-influenza medications—oseltamivir, zanamivir, amantadine, and rimantadine—should be viewed as contraindicated in pregnant women during a pandemic. Selection of anti-influenza medications should be primarily guided by resistance patterns and by medication availability, issues that may change as a pandemic evolves. Assuming that the virus is susceptible, oseltamivir is preferred for treatment of pregnant women, given its systemic absorption; the active metabolite of oseltamivir is maintained at high levels in plasma and appears to be well distributed to all tissues.³⁹ However, the drug of choice for prophylaxis is less clear. Zanamivir may be preferable because of its limited bioavailability; however, respiratory complications that may be associated with zanamivir because of its inhaled route of administration need to be considered,³⁰ especially in women at risk for respiratory problems, such as asthma.

No data are available to suggest that this guidance should be altered by pregnancy trimester. Unpublished data from a study that used very high doses of

TABLE 1—Antipyretic Medications and Their Effects During Pregnancy

Medication (Category) ^a	Effects on Fetus
Aspirin (C in first and second trimesters; D in third trimester)	First-trimester exposure not associated with overall increase in risk of defects, inconsistent associations with various specific defects ²² Increased risk for gastroschisis identified in several studies ²³ Late exposure (within a week of delivery) associated with abnormalities in hemostasis in mother and infant ^{22,24}
Acetaminophen (B)	First-trimester exposure not associated with overall increase in risk of defects ²⁵ No increased risk for most specific defects found in some studies, but inconsistent associations with some defects (eg, gastroschisis, amniotic band sequence) ²²
Ibuprofen (B in first and second trimesters; D in third trimester)	Third-trimester exposure associated with premature closure of the ductus arteriosus ²² First-trimester exposure to prescription ibuprofen not associated with overall increased risk of defects, but few studies of over-the-counter ibuprofen are available ²² Few specific defects studied; no increased risk for some (eg, neural tube defects), but inconsistent associations with others (eg, septal heart defects) ²²

^aThe Food and Drug Administration assigns pregnancy-related drug risks to 5 categories. Category A: adequate, well-controlled studies in humans have not shown an increased risk of fetal abnormalities. Category B: animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Category C: animal studies have shown an adverse effect, and there are no adequate and well-controlled studies in pregnant women, or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Category D: adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus; however, the benefits of therapy may outweigh the potential risk. Category X: adequate well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities; use is therefore contraindicated in women who are or may become pregnant.

oseltamivir to treat juvenile rats led to a recommendation to avoid oseltamivir treatment in infants younger than 1 year,^{27,28} although a small study showed no adverse effects among 47 infants younger than 1 year who were treated with oseltamivir.⁴⁰ These results may suggest a risk in late pregnancy; however, given the significant risk of influenza complications late in pregnancy and the high dose used in the animal model, the benefits of oseltamivir appear to outweigh potential risks. No data are available to address whether dosage adjustment is needed; thus, no dosage alterations for pregnant women are recommended at this time.

For anti-influenza medications to be most effective they must be

given early in the course of illness; thus, treatment should not be withheld while waiting for results of diagnostic testing. However, clinicians may consider linking the results of diagnostic testing to treatment if highly sensitive and specific rapid influenza tests are available. If a highly sensitive test demonstrates that a pregnant woman is not infected with the pandemic influenza virus strain and prophylaxis is not recommended because of exposure, discontinuation of anti-influenza medications is logical, because of the lack of benefit of these medications when an influenza diagnosis is not confirmed and because of issues related to medication availability. Currently available rapid diagnostic tests do not have

sufficient sensitivity to reliably rule out influenza virus infection. A positive test can be useful for deciding whether to recommend treatment and might be helpful in convincing women to accept treatment if they are concerned about the potential for antiviral toxicity. However, when a community outbreak of influenza is confirmed, it is reasonable to treat everyone presenting with acute febrile respiratory illness, including pregnant women, because it facilitates rapid decision-making and is likely to be more cost efficient.

VACCINATION

Vaccination is the most effective method for preventing

severe influenza illness and its sequelae,³⁸ and once available in an influenza pandemic, vaccination will be an important component of the public health response.⁴¹ The federal government's guidelines place pregnant women in the highest-priority group to receive vaccination for all levels of pandemic severity.⁴² However, a vaccine is not expected to be available at the beginning of a pandemic; until it is, other strategies (eg, nonpharmaceutical interventions) will play a critical role.

For seasonal influenza, trivalent inactivated vaccine is approved for everyone aged six months or older and is recommended by the Advisory Committee on Immunization Practices for pregnant women. By contrast, live, attenuated influenza vaccine is approved only for healthy nonpregnant persons aged 2 to 49 years. The advisory committee,³⁸ the American College of Obstetricians and Gynecologists,³⁷ and other professional organizations recommend that all women who are pregnant during influenza season receive trivalent inactivated vaccine, regardless of pregnancy trimester.

Despite this guidance, influenza vaccination coverage remains low among pregnant women, with 13% of pregnant women in the United States reporting receiving the vaccine during the 2006 to 2007 influenza season, excluding pregnant women who reported high-risk conditions such as diabetes, heart disease, or lung disease.³⁸ The immunogenicity of seasonal influenza vaccine among pregnant women is not expected to differ from that among nonpregnant adults.⁴³ However, low vaccination rates for seasonal influenza among pregnant women, combined with exclusion of pregnant

TABLE 2—Anti-influenza Medications and Their Effects During Pregnancy

Medication	Effects on Fetus
Oseltamivir	Animal data for rats and rabbits show pregnancy loss at high doses, no increased risk of malformations ²⁶ ; studies in 7-day-old rats with much higher doses (1000 mg/kg) than would be used for treatment of humans found neurologic toxicity, but these effects were not observed in 14-day-old rats given even higher doses. Results were attributed to the immature blood-brain barrier. ^{27,28} Human data (61 cases) show mostly normal outcomes, but 4 spontaneous abortions and 6 pregnancy terminations reported in postmarketing period as well as single cases of trisomy 21 and anencephaly. ²⁹
Zanamivir	Animal data (rat, rabbit) show no evidence of embryotoxicity or increased risk of malformations. ²⁶ Human data available for 3 pregnancies during clinical trials (1 spontaneous abortion, 1 elective termination, 1 normal outcome). ³⁰
Amantadine	Animal data for rats given 6–12 times the human dose show increased fetal death and malformations; data for rabbits given 1–12 times the human dose show no increase in malformations. ^{31,32} Human data show malformations in 5 (7.8%) of 64 infants born after prescription in first trimester (4.8% expected). ³³ Case reports reveal heart and limb defects. ^{34,35}
Rimantadine	Animal data for rats given 125 times the human dose show no increase in malformations but increased embryonic death ²² ; data for mice given 75 times the human dose show no increase in malformations. ²² No human data published.

women from many vaccine clinical trials, result in a paucity of data to inform decisions before a pandemic.

Documented adverse effects of seasonal influenza vaccination among pregnant women have not differed from those in the general population. Because vaccination with inactivated agents during pregnancy is believed to be safe, trivalent inactivated vaccine presents less theoretical concern than live, attenuated influenza vaccine. Furthermore, neither cohort studies^{44,45} nor the Vaccine Adverse Event Reporting System, a surveillance system that collects data on adverse events observed after use of vaccines,⁴⁶ have found any significant increase in adverse maternal or infant outcomes among vaccinated pregnant women, although these data have limitations that affect interpretation. More data are needed on the safety and effectiveness of seasonal influenza vaccination among pregnant women.

Monitoring influenza vaccine use during pregnancy for effectiveness and safety in the event of a pandemic will be critical. Investigators should build on existing monitoring mechanisms to evaluate the short-term (e.g., vaccine effectiveness) and long-term maternal and pregnancy outcomes following vaccination, although initiating such surveillance during a pandemic will be difficult. Some possible existing mechanisms for monitoring vaccine safety include the Vaccine Adverse Event Reporting System⁴⁷ and the Vaccine Safety Datalink project,⁴⁸ which uses health maintenance organization data. However, it should be noted that systems that rely on electronic record capture, such as the Vaccine Safety Datalink project, will be unlikely to ascertain vaccine that is distributed through public health clinics.

Although the vaccine initially available in a pandemic might be distributed through public health agencies, support for

vaccinating pregnant women from their established health care providers will be critical. Professional organizations such as the American College of Obstetricians and Gynecologists, the Society for Maternal–Fetal Medicine, and the American Academy of Family Physicians should urge all pregnant women to receive pandemic influenza vaccine in whatever setting is available. It will also be critical to develop mechanisms by which information about vaccination can be provided to pregnant women without requiring office visits or other potential exposure to influenza.

In this pre-pandemic period, efforts to improve uptake of seasonal influenza vaccine among pregnant women need to be implemented. Because these efforts would familiarize women and their health care providers with recommendations for influenza vaccine during pregnancy through their implementation during annual epidemics,

they could improve uptake of influenza vaccine during a pandemic.

NONPHARMACEUTICAL INTERVENTIONS AND HEALTH CARE PLANNING

The Centers for Disease Control and Prevention, in collaboration with other federal agencies and partners in public health, education, business, health care, and the private sector, has developed interim planning guidance on the use of nonpharmaceutical interventions to mitigate an influenza pandemic.⁴⁹ Although pregnant women are at increased risk for morbidity and mortality from influenza and possibly at increased risk of exposure (because of their interactions with young children), no evidence suggests that implementation of community mitigation strategies should be altered for pregnant women. In addition, pregnant women should follow the same guidance as the general population regarding infection control measures such as use of masks and other personal protective equipment, cough etiquette, and hand hygiene.⁵⁰

Regarding occupational exposure, in general, pregnant women working in professions where they are exposed to asymptomatic—but high-risk—persons should follow the same guidance as all persons and should carefully follow recommended infection control procedures. However, for pregnant women working in high-risk professions involving direct contact with known influenza patients (e.g., a nurse or physician caring for hospitalized patients), employers may consider reassignment to lower-risk activities, such as telephone triage.⁵¹

Other important considerations include the capacity of health care

systems to handle patient visits during an influenza pandemic and the effects of nonpharmaceutical interventions on the interaction of pregnant women with the health care system. The needs of women to receive medical services during pregnancy and the intrapartum period, while concomitantly minimizing their exposure to influenza, must be addressed in pandemic planning.

An important issue is whether routine prenatal and obstetric care should be altered to limit exposure of healthy pregnant women to sick patients. During a pandemic, consideration should be given to reducing the number of recommended prenatal visits for low-risk pregnancies.⁵² Home monitoring of blood pressure, weight, urine protein and glucose, and symptoms could be an alternative to some prenatal care visits in select low-risk patients. Furthermore, enhanced virtual prenatal care, including online pregnancy education resources and real-time support from experienced, trained health care providers via telephone or computer, could be used to supplement prenatal care. Telephone triage capabilities should also be enhanced to prevent women from coming to the clinic or hospital unnecessarily. Trusted, highly skilled health care providers could be more effective in reassuring patients and reducing the number of unnecessary patient visits than would other providers. With possible disruption in usual health care delivery systems during a pandemic, women should be provided with copies of their medical and prenatal care records. This information could be condensed on a prenatal care card, similar to that developed by the World Health Organization.⁵³

During a pandemic, hospitals need to plan for deliveries of babies to well women and to mothers who are sick with influenza. Ideally, as was done during the SARS (severe acute respiratory syndrome) epidemic,^{54,55} separate hospitals with separate entrances and air-handling systems should be designated for delivery of infected and uninfected patients, but in many communities this option may not be feasible. Having separate suites for labor and delivery and for postpartum care for infected and uninfected women within the same hospital will be a more practical option in some settings. Alternative delivery sites with easy access to emergency services may also be considered. These sites, which should be capable of providing timely and comprehensive emergency medical and surgical services, may include free-standing ambulatory surgical centers and local trailer units stationed outside of hospitals. Given the findings of increased pregnancy loss⁴ and the high rates of preterm delivery⁵⁶ during the 1918 pandemic, the need for resources for preterm births may be increased.⁵⁷

COMMUNICATIONS

Health communicators and preparedness planners face numerous challenges when considering which messages and channels are most appropriate for providing pregnant women with targeted information about pandemic influenza preparedness and response. Little information exists about how pregnancy status and women's roles and responsibilities might affect the adoption of recommendations for preparedness or response. Pregnant women with caregiving responsibilities for young children and with

head-of-household responsibilities might find it difficult to implement social-distancing strategies designed to reduce their exposure risk. Some women and health care providers might be resistant to the use of vaccination and pharmacologic interventions because of concerns for the fetus, and specific recommendations for treatment and care will change as a pandemic evolves. Finally, marked changes in health care delivery are anticipated during a severe influenza pandemic, likely requiring changes in both routine and emergency health care delivery and facility accessibility.

Although the challenges are many and complex, there are several opportunities for health communications directed toward pregnant women and their families. Pregnant women appear to be highly motivated to make healthy decisions.⁵⁸ Health care providers are often trusted sources of information,^{59,60} and because pregnant women typically have multiple contacts with health care providers during pregnancy, the health care visit will be critical for providing pandemic influenza guidance. Many cultures view pregnancy as a time when a woman's health and well-being are priorities and a time when women are highly motivated to initiate healthy behaviors. Supportive family members, friends, and formal social networks such as faith-based communities can serve as communication avenues and could also have roles in alternative care strategies. Workplaces, community social organizations, and retail and service venues can also be considered as resources for reaching pregnant women.

During a pandemic, it is essential that pregnancy communication strategies remain flexible as new information arises. Furthermore, specific guidance might be

different for women who differ in stage of pregnancy, health and risk status, locality, and other vulnerabilities, such as language barriers, homelessness, or chronic illness. Although the behaviors to promote—and the message concepts used to promote these behaviors—will be universal, communicators will need to tailor messages for some groups of pregnant women. Cultural, religious, socioeconomic, and other factors will influence the communication approach, materials used, and choice of distribution channels to effectively communicate the appropriate messages.

Because approximately half of all pregnancies in the United States are unplanned,⁶¹ it may be useful to expand communication strategies to target all women of reproductive age. During a pandemic, communicators can use existing approaches aimed at reaching women with small children. For example, Medicaid and the Special Supplemental Nutrition Program for Women, Infants, and Children serve women who may be pregnant. Communication strategies should be developed to take advantage of these existing communication frameworks.

CONCLUSIONS

Experts and external partners convened at the Pandemic Influenza: Special Considerations for Pregnant Women meeting to review the available evidence regarding care of pregnant women during an influenza pandemic. The group supported treatment of influenza-associated fever with acetaminophen and advised no alteration in the recommendations for treatment and prophylaxis with anti-influenza medications used for other high-risk populations. Pregnant women are considered a high-priority group for

receipt of vaccine. However, seasonal influenza vaccine coverage is low among pregnant women, and improving their coverage with seasonal influenza vaccine may improve vaccine uptake in a pandemic. Generally, nonpharmaceutical interventions should be implemented in the same manner for pregnant women as for the general population.

Planning for inpatient and outpatient obstetric care in the event of a pandemic needs to be initiated before a pandemic. Health care facilities, public health agencies, and individual health care providers will need to work together to develop these plans. Communication messages and channels should be tailored to reach pregnant women and promote behaviors specific to their needs.

Several gaps remain in the data needed to inform plans to prepare pregnant women for an influenza pandemic. Improved information on the effects of influenza on the fetus and on the effectiveness, pharmacokinetics, and safety of anti-influenza medications during pregnancy is urgently needed. Strategies should be developed to share clinical information during a pandemic, and mechanisms for collecting data on pregnancy outcomes after infection with influenza, treatment with anti-influenza medications, and receipt of influenza vaccine during a pandemic should be established in advance. Additional data will need to be incorporated into planning efforts as a pandemic progresses, including information on the virulence of the pandemic virus, risk stratification for exposure, viral resistance to anti-influenza medications, availability of anti-influenza medications and vaccine, and effects of medications on pregnant women and fetuses. More data on the safety and effectiveness of seasonal

influenza vaccination during pregnancy and a better understanding of how to overcome the barriers to vaccination of pregnant women are needed.

Understanding the knowledge, attitudes, and behaviors regarding influenza and emergency preparedness of women who are pregnant or of reproductive age will be important to guide communication planning. Addressing these issues will be necessary to ensure that pregnant women receive appropriate guidance and health care in the event of an influenza pandemic. ■

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This brief was accepted December 29, 2008.

Contributors

All authors planned the meeting, reviewed the relevant literature, and reviewed drafts of the article.

Acknowledgments

Financial support for the meeting was provided by the Influenza Coordination Unit, the Division of Reproductive Health, and the Division of Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC); the Association of Maternal and Child Health Programs; and the March of Dimes.

We are especially grateful to planning committee members Hani Atrash, William Callaghan, Jamylle Gilyard, Cynthia Moore, Jill Pace, Samuel Posner, and John Seggerson, CDC, Atlanta, GA, who helped develop the meeting agenda and identified meeting speakers and participants;

to Michael Fraser and Helen Cedano, Association of Maternal and Child Health Programs (AMCHP), Washington, DC, who provided logistical guidance and support for the meeting; and to Marie Murray, SoWrite, Atlanta, GA, who provided a written meeting summary.

We thank the other meeting participants who contributed to this work: William Andrews, University of Alabama at Birmingham; Kate Arnold, Georgia Division of Public Health, Atlanta; Debra Blog and Kim Noyes, New York State Department of Health, Albany; Stacey Cunningham, AMCHP; Anne Dunlop, Emory University School of Medicine, Atlanta, GA; Cynthia Grant, Department of Human Resources, Division of Public Health, Atlanta, GA; Carol Hogue, Emory University; Iffath Hoskins, American College of Obstetricians and Gynecologists and Lutheran Medical Center, Brooklyn, NY; Alan Kendal, Emory University, Atlanta, GA; Linda Lewis, Food and Drug Administration, Silver Spring, MD; Matthews Mathai, World Health Organization, Geneva, Switzerland; James Ransom, National Association of County and City Health Officials, Washington, DC; Mitchell Rothholz, American Pharmacists Association, Washington, DC; Ellen Schleicher, Association of State and Territorial Health Officials, Arlington, VA; and Catherine Spong, National Institute on Child Health and Human Development, Bethesda, MD.

Other participants from the CDC included Nelson Arboleda, Wanda Barfield, Karen Bouye, Carolyn Bridges, Maleeka Glover, Seema Gupta, Sonja Hutchins, Nadine Shehab, Natasha Singh, Christa-Marie Singleton, Dixie Snider, Lynn Sokler, Timothy Uyeki, Hoang Vu, and Alicia Williams.

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Dallas; and Tom Shimabukuro, Toscha Stanley, and Carla White, CDC.

Note. The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of CDC. Moreover, this article includes statements made by individuals at a meeting convened by the CDC for the purpose of obtaining their input. Such statements also do not necessarily represent the views of CDC.

Human Subjects Protection

No protocol approval was necessary because data were obtained from secondary sources.

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